Citation:

Kaushik S, Wang JJ, Wong TY, Flood V, Barclay A, Brand-Miller J, Mitchell P. Glycemic index, retinal vascular caliber and stroke mortality. *Stroke.* 2009 Jan; 40 (1): 206-212. Epub 2008 Oct 23.

PubMed ID: 18948616

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

- To investigate associations of glycemic index with stroke-related mortality and retinal microvascular caliber in an older Australian cohort
- To test the hypothesis that retinal microvascular changes may partly explain the reported association between high glycemic index foods and stroke mortality
- To examine associations with dietary cereal fiber given its strong interrelationship with glycemic index.

Inclusion Criteria:

- Blue Mountains Eye Study participants
- Population-based cohort aged 49 years and older.

Exclusion Criteria:

- Subjects were excluded when more than 12 food-frequency questionnaire (FFQ) questions were missing, if an entire page was blank, or if daily energy intakes were <2,500kJ or >18,000kJ
- Subjects were excluded due to missing retinal photographs or poor photographic images.

Description of Study Protocol:

Recruitment

- Blue Mountains Eye Study is a population-based cohort study of vision, common eye diseases and other health outcomes in an urban, predominantly white population aged 49 years and older
- The 1992 to 1994 baseline study examined 3,654 eligible residents of two post codes of the Blue Mountains region west of Sydney, Australia (82.4% response)
- Subsequent five- and 10-year examinations of this cohort were conducted.

Design

Prospective cohort study.

Dietary Intake/Dietary Assessment Methodology

Glycemic index measured through validated 145-item FFQs modified for the Australian diet, from a Willett questionnaire incorporating a nine-category frequency scale and standard portion estimates.

- Dietary intakes and mean glycemic index calculated using the Australian Tables of Food Composition database
- 88.9% of glycemic index values were obtained from published values and 11.1% were interpolated from similar food items.

Blinding Used

Not applicable.

Intervention

Not applicable.

Statistical Analysis

- Associations between dietary variables and retinal vessel caliber data are cross-sectional, the mortality associations are longitudinal
- Subjects intakes were divided into tertiles by their mean dietary glycemic index or fiber intake, and dietary glycemic index and fiber variables were adjusted for total energy intake by the Willett residual method
- Cox proportional hazards regression was used to assess hazard ratios with 95% confidence intervals (CI) for tertile of mean glycemic index or cereal fiber consumption on 13-year stroke mortality after adjustments
- To determine the individual and joint effects of glycemic index and cereal fiber on the risk of stroke, the population was stratified into three groups by unhealthy vs. healthy dietary intakes
- Mean venule-adjusted arteriolar caliber and arteriole-adjusted venular caliber for glycemic index or cereal fiber tertile was assessed using ANCOVA
- Logistic models were used to assess interactions between fiber consumption and glycemic index in their effects on the retinal microvasculature using the widest venular quintile as the outcome variable.

Data Collection Summary:

Timing of Measurements

- Participants completed FFQs and were interviewed at baseline (1992-1994)
- Mortality data reviewed over 13-year follow-up period in December 2005.

Dependent Variables

- Retinal arteriolar and venular diameters were measured from photographs
- Stroke mortality data were derived using the Australian National Death Index.

Independent Variables

- Glycemic index measured through validated 145-item FFQs modified for the Australian diet, from a Willett questionnaire incorporating a nine-category frequency scale and standard portion estimates
- Dietary intakes and mean glycemic index calculated using the Australian Tables of Food Composition database
- 88.9% of glycemic index values were obtained from published values and 11.1% were interpolated from similar food items.

Control Variables

- Age
- Gender
- Blood pressure
- BMI
- Smoking
- Educational qualifications
- Fair or poor self-rated health
- Diabetes mellitus
- History of coronary heart disease
- Vegetable consumption
- Saturated fat
- Fish consumption
- Nutrient variables: Vitamins C and E, β-carotene, zinc and folate
- Fasting blood samples analyzed for hemoglobin, white cell and platelet counts, glucose, total cholesterol, triglycerides, HDL-cholesterol and fibrinogen.

Description of Actual Data Sample:

- *Initial N:*
  - 3,654 baseline participants
  - 3,267 participants attempted and returned the FFQ
- *Attrition (final N):*
  - 2,897 participants with sufficiently complete and plausible FFQs
  - A further 185 participants were excluded due to missing retinal photographs
- *Age:* 49 years or older at baseline
  - Glycemic index tertile 1: Mean age 64.8 years, 30.6% male
  - Glycemic index tertile 2: Mean age 65.6 years, 44.6% male
  - Glycemic index tertile 3: Mean age 65.7 years, 56.7% male
- *Ethnicity:* Predominantly White
- *Other relevant demographics:* None
- *Anthropometrics:* None
- *Location:* Australia.

Summary of Results:

Key Findings

- Over 13 years, 95 of 2,587 participants (3.5%) died from stroke
- Increasing glycemic index (hazard ratio=1.91, 95% CI: 1.01-3.47, highest vs. lowest tertile) and decreasing cereal fiber (hazard ratio=2.13, 95% CI: 1.19-3.80, lowest vs. highest tertile) predicted greater risk of stroke death adjusting for multiple stroke risk factors
- There was no relationship between total, vegetable or fruit fiber and risk of stroke-related death
- Persons consuming food in the highest glycemic index tertile and lower cereal fiber tertile had a five-fold increased risk of stroke death (hazard ratio=5.06, 95% CI: 1.67-15.22)
- There was a higher risk of all-cause mortality in persons with both a higher glycemic index and low cereal fiber diet (hazard ratio=1.48, 95% CI: 1.11-1.98)
- Increasing glycemic index and decreasing cereal fiber were also associated with retinal venular caliber widening (P for trend <0.01)
- Adjustment for retinal venular caliber attenuated stroke death risk associated with high glycemic index by 50% but did not affect the risk associated with low cereal fiber consumption.

Author Conclusion:

- Diets with high glycemic index and low cereal fiber content predicted greater stroke mortality. These diets were also associated with wider retinal venular caliber, an intermediate microvascular marker of stroke
- The increased risk of stroke mortality associated with high-glycemic index diets was attenuated by 50% after accounting for variations in retinal venular caliber
- Although microvascular changes are known to precede cardiovascular events, these findings indicate that the deleterious cerebrovascular effects from high glycemic index diets could operate partly by anatomic effects on the cerebral microvasculature.

Reviewer Comments:

- *Long follow-up period of 13 years*
- *Dietary intake only measured at baseline*
- *Authors are directors/consultants for not-for-profit glycemic index-based food endorsement programs*
- *Authors note the following limitations:*
  - *Cross-sectional nature of the associations of glycemic index and vessel caliber*
  - *Incomplete control for confounding effect from unmeasured social factors may have occurred*
  - *Relatively low sensitivity and specificity of death certificate data could have tended to misclassify some stroke deaths.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A

2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes

3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	N/A
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A

6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	N/A
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes

9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	???
10.1.	Were sources of funding and investigators' affiliations described?	No
10.2.	Was the study free from apparent conflict of interest?	???